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(54) Title: COMPOSITIONS AND METHODS FOR TREATMENT OF SKIN DISORDERS

(57) Abstract: The present invention concerns methods and compositions for prophylactic or therapeutic treatment of skin disorders by administering therapeutically or prophylactically effective amounts of a probiotic. The present invention is also concerned with the treatment of symptoms of skin disorders.

COMPOSITIONS AND METHODS FOR TREATMENT OF SKIN DISORDERS

TECHNICAL FIELD

The invention relates to the field of skin disorder prevention and/or treatment, and in particular to probiotic bacteria and compositions containing same, which are useful in the prevention and/or treatment of skin disorders.

BACKGROUND ART

Skin disorder such as dermatitis is an inflammatory condition of the skin characterised by erythema and pain or pruritis. Dermatitis is a heterogeneous group of skin disorders and various cutaneous lesions occur, each being potentially unique to a particular allergen, disease or infection. In many instances food or environmental factors may be the trigger however there are numerous skin conditions for which the cause or initial trigger are not known or which may be initiated by for example an allergen or an antigen but which persist despite preventing or discontinuing exposure to the allergen or antigen. Dermatitis may be chronic or acute and the treatment is usually specific to the cause, if known, or to the condition.

An example of a skin disorder of unknown cause is rosacea. This disorder may be defined as an inflammatory condition of the skin, presenting with a history of flushing and/or blushing along with clinical findings of erythema, edema, telangiectasia, papules, pustules, and nodules primarily of the face. Rosacea cannot be cured at present but popularly prescribed medical treatments for the condition include oral antibiotics such as tetracycline (1) and topical treatments such as 0.75% and 1.0% metronidazole gel (2, 3). Both these treatments have proved to maintain remission of moderate to severe rosacea. Other alternative treatments include isotretinion (accutane), a synthetic oral retinoid, which has been shown to produce results in patients who have been unresponsive to common forms of treatment for rosacea (4, 5).

Other skin conditions involving lesions with similar characteristics may in fact have a different cause and thus require different conventional treatment approaches. Whatever the cause of dermatitis, it is of great discomfort to the sufferer and treatment is often aggressive and may be associated with significant side effects.

Another example of a skin disorder which may be difficult to treat and which has a variety of causes is contact dermatitis, which may be triggered in sensitive subjects by skin contact with an external stimulus/agent. For example domestic animals frequently develop dermatitis of one type or another. Most commonly in dogs it is flea-induced dermatitis, which can progress to more severe skin infection if not treated rapidly. Hypersensitivity in dogs, especially to flea bite, is a major reason for the presentation of animals to community-based veterinary clinics. These animals are routinely treated with anti flea products, containing pesticides, and topical corticosteroids. Unfortunately these treatment options are less than ideal as fleas develop resistance to pesticides and prolonged use of corticosteroids carries with it the ever-present risk of Cushing's disease. A similar skin condition in humans may be triggered by house dust mite and represents a skin disorder arising from contact of skin with a substance or an agent capable of inducing an adverse reaction.

Clearly, alternative therapeutic options are required for skin disorders which may not have a known cause, are particularly difficult to treat or for which current therapies have significant limitations, or skin disorders arising from external contact with an antigen, an allergen or an agent capable of causing an adverse skin reaciton

There is therefore a need for improved treatments, whether prophylactic or therapeutic, for skin disorders such as those described above.

It is an object of the present invention to overcome or ameliorate at least one of the disadvantages of the prior art, or to provide a useful alternative.

SUMMARY OF THE INVENTION

It has been unexpectedly found that certain probiotic bacteria, when administered to human subjects or animals in sufficient quantity, have the ability not only to down-regulate systemic and peripheral markers of inflammation and/or allergy but also to treat skin disorders which until now were difficult to treat or required therapeutic approaches which were associated with significant side-effects and variable efficacy. Further, the probiotic compositions of the present invention are also effective in treating skin disorders arising from contact of skin with a substance or an agent capable of causing a hypersensitivity or other adverse reaction.

According to one aspect the present invention provides a method for prophylactic or therapeutic treatment of a skin disorder by administering to a subject requiring such treatment a therapeutically or prophylactically effective amount of a probiotic.

According to another aspect the present invention provides a method of treatment of one or more symptoms of skin disorder by administering to a subject requiring such treatment an effective amount of a probiotic.

Preferably the skin disorder is dermatitis having associated therewith visible lesions. Even more preferably it is contact dermatitis, seborrheic dermatitis, actinic dermatitis, dermatitis caused by microbial infection and the like. A specific example of as particularly preferred skin disorder which can be treated by the methods of the present invention is rosacea. Another skin condition which can benefit from the treatment of the present invention is eczema. In mammals other than humans, for example domestic pets such as dogs, the preferred skin condition which can be treated by the methods and compositions of the present invention is flea-induced dermatitis. However, similar conditions in human subjects, for example house dust mite induced dermatitis or contact dermatitis, may also be treated by the methods and compositions of the present invention

Preferably the symptoms of dermatitis which can be treated by compositions and methods of the present invention are selected from pruritis, pain and erythema.

Preferably, the probiotic is a lactic acid bacterium and even more preferred is *Lactobacillus fermentum* or *Lactobacillus acidophilus*. The most preferred strain of *L. fermentum* is the VRI-002 strain (obtained from University of New South Wales, Microbiology Culture Collection, Sydney, New South Wales, Australia; also deposited with Australian Government Analytical Laboratories, AGAL, of PO Box 385, Pymble NSW2073, Australia, on 12 December 2002 and given the accession number NM02/32959).

According to a further aspect the present invention provides a method of lowering levels of one or more immune markers of allergy and/or inflammation in a subject with dermatitis having elevated levels of said markers, by administering to a subject requiring such treatment an effective amount of a probiotic

Preferably the immune markers are selected from immunoglobulins and/or cytokines characteristic of allergic responses or of Th1 and Th2 T cell responses. For example suitable markers can be chosen from IgE, IL-4, IL-10, IL-12, interferon gamma, and the like.

Preferably, the probiotic is part of a composition, such as for example a food preparation, food supplement or a pharmaceutical preparation (eg, tablets, capsules, powders, liquid formulations and the like). The probiotic, or the composition containing said probiotic, may be administered by any known means but preferably it is administered orally. The probiotic, or the composition containing said probiotic, may also be advantageously administered topically, either by application to a mucosal surface, or by application directly to the affected skin areas.

It is also preferable that the probiotic, or the composition containing said probiotic, is administered at the onset of dermatitis or other skin disorder, or shortly thereafter. However, established skin lesions and conditions can be effectively treated by the methods of the present invention, as demonstrated in the examples.

The probiotic, or the composition containing said probiotic, may be administered in conjunction with one or more pharmaceutically active agents normally used for treatment of dermatitis. The probiotic, or the composition containing said probiotic, may be administered simultaneously (co-administered) with the other treatments or it may be administered sequentially in any order.

Preferably, the subject to be treated is selected from those subjects who are at high risk of exposure to allergens and/or antigens, or other agents, which may cause dermatitis, or individuals who have a family history or a genetic predisposition to developing dermatitis. Of course subjects already exhibiting overt signs of dermatitis, or having well advanced dermatitis can also advantageously be treated by the methods of the present invention.

The terms "subject" and "individual" are used interchangeably and in the context of the present invention include in their scope any mammal which can develop, or already has, dermatitis of whatever cause. Of course the preferred subjects for administration of the treatment of the present invention are humans, domestic pets and farm animals.

Preferably the amount of probiotic bacteria administered to a human subject is at least 10^{10} bacteria. More preferably the amount administered is from about 10^{10} to about 10^{12} bacteria. The dosage may be administered daily as a single dose or may be divided into two or more doses to be taken at different intervals through the day. The treatment may be administered for short periods of time such as several days to several weeks, or it may be administered for prolonged periods of time such as months or years. It may also be administered in a life-long maintenance protocol. Intermitent dosage regime is also contemplated which may involve administration less frequent than daily, for example once, twice or three times per week, or similar dosage regime.

The required dosage amount will vary according to the severity of dermatitis, the cause of the condition, age of the subject and other standard clinical parameters which can be easily determined by routine procedures within the skill-set of those skilled in the art.

It is preferred that the probiotic or a composition containing the probiotc, be administered daily. Of course, it can be administered several times per day, or it may be administered infrequently (for example every second or third day), depending on the progress of treatment of dermatitis, its cause and severity. These parameters can also be easily determined by those skilled in the art.

According to yet another aspect the present invention provides a use of a probiotic for the manufacture of a medicament for treating dermatitis or other skin disorders.

According to another aspect the present invention provides a dermatological composition comprising a therapeutically and/or prophylactically effective amount of probiotic, together with a pharmaceutically acceptable carrier, adjuvant, solvent or excipient.

Preferably the probiotic is a lactobacillus and more preferably it is *L. fermentum*. Even more preferred is *L. fermentum* VRI-002 strain.

The dosage form is preferably a tablet or a capsule, but it may also be a powder, liquid or paste/gel.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. Mean VAS scores in dogs A and B for i) panniculus, ii) back arching and iii) involuntary scratching in response to oral administration of *L. fermentum* VRI-002. (Score: 0-Negative 1-low reactivity 2-moderate reactivity 3-high reactivity).

DESCRIPTION OF THE PREFERRED EMBODIMENT

Whereas it may be expected that oral administration of probiotics could assist in food borne allergy treatment or treatment of GI tract infections, such an expectation is not realistic or appropriate when considering the treatment of skin conditions which are not associated with the oral intake of any particular infectious agent or allergen. The methods and compositions of the present invention have been developed for human and veterinary applications in the treatment of various forms of skin conditions, including dermatitis, and in particular skin conditions which have no known origin or trigger, or skin disorders which are difficult to treat or currently require treatments associated with significant side-effects. Whether used for treatment of humans or domestic animals, the underlying principles are the same and advantageously the treatments of the present invention may be used irrespective of the cause of the skin condition or dermatitis.

Typically, the formulations containing probiotic bacteria, such as *Lactobacillus fermentum* VRI-002 strain, are administered orally. In the case of administration to a human subject, the dosage is in the form of capsules given twice daily. Typically the effective daily dosage is in the range of about 10^8-10^{12} bacteria and frequency of administration is once or twice daily. If treating animals such as dogs and cats, the appropriate dosage can be introduced in and/or with food.

The probiotic bacteria can be formulated into various compositions, both for veterinary and pharmaceutical use, typically capsules, tablets, powders, pastes and the like. Such formulations can be prepared by known means, using pharmaceutically acceptable carriers, excipients, solvents or adjuvants. Such procedures and ingredients are well know and amply described in standard texts and manuals, for example "Remington: The Science and Practice of Pharmacy",

1995, Mack Publishing Co. Easton, PA 18042, USA, which is incorporated herein by reference.

The probiotic bacteria may also be formulated into food or feed products and food or feed supplements by the usual well-known means. Such products are most suited for administration to animals such as domestic pets or farm animals.

The methods and compositions of the present invention are useful for

(1) treatment of skin disorders which have basis in, or are mediated by, a component of the immune system.

(2) treatment specifically of dermatitis of diverse aetiology

(3) treatment of dermatitis in all mammals, including humans, domestic pets and farm animals, particularly of dermatitis caused by skin contact (eg. contact dermatitis)

(4) prophylactic treatment of mammals in the prevention of occurrence or re-occurrence of dermatitis, particularly in subjects exposed to environments which may cause dermatitis or those who may be predisposed to developing dermatitis.

The invention will now be described more particularly with reference to non-limiting examples.

EXAMPLES

Example 1: Preparation of *Lactobacillus fermentum*

Typically the *L. fermentum* (VRI-002) was grown under industrial conditions in the following medium:

Yeast extract (20g), tryptone (0.5g), sodium acetate (1g), disodium hydrogen phosphate (Na2HPO4.2H2O; 0.2 g), potassium dihydrogen phosphate (0.7g), magnesium sulphate (MgSP4.7H2O; 0.7g), manganese sulphate (MnSO4.H2O; 0.06g), calcium chloride (0.05g), ferrous sulphate (FeSO4.7H2O; 0.005g), glucose (30g) and water (make up to one litre). After growth, cells were harvested by centrifugation and the slurry freeze dried using conventional cryoprotectants, according to known and well established methodology. The preparation of *L. fermentum* may be used immediately or stored for future use.

Example 2: Case study 1 – treatment of rosacea in a human subject.

A male subject with a long history of rosacea, was treated with *L. fermentum* (VRI-002 strain). The subject was already receiving antibiotics at the time of initiation of treatment with *L. fermentum*.

The subject was treated twice daily, in the morning and at night, with 2 capsules on each occasion, each capsule included 7×10^9 colony forming units (cfu's) of *L. fermentum*. The total daily dosage being 2.7×10^{10} cfu's of *L. fermentum* .

The subject ceased to take all medication apart from the *L. fermentum,* 2 weeks prior to the doctor visit. At the visit, the rosacea had visibly improved in absence of antibiotics which were prescribed for the treatment of the condition. On cessation of *L. fermentum* treatment the condition returns but is suppressed with regular administration of *L. fermentum.*

Example 3: Case study 2 – treatment of flea-induced dermatitis in dogs.

The aim of this study was to determine whether the oral administration of a particular probiotic strain of *Lactobacillus fermentum*, designated VRI-002, would reduce the clinical signs and symptoms of skin conditions induced by external contact of skin with an agent capable of or known to cause adverse skin reactions, such as contact dermatitis or the like. The model used for this purpose is flea-induced dermatitis in dogs.

Two household dogs (a Neopolitan Mastif and a Boxer-cross, mean weight 20-56 kg) living in the same household were chosen for the study. At the start of the experiment both animals exhibited numerous clinical signs of dermatitis, in particular intense pruritis, namely scratching, biting, alopecia at the base of the tail (one dog only). Both dogs were fed the same diet and lived together under identical conditions. The dogs were fed 10 mL of UHT skim milk using a 20 mL syringe containing *Lactobacillus fermentum* (prepared as described in example 1), at 5×10^9 cfu daily (single dose) for 14 days with their evening meals. 10 mL of blood was collected before treatment and 3 days after treatment had ceased, for IgE and cytokine determination.

Clinical examinations by a qualified and practising veterinarian were performed each evening, immediately after the meal. The symptomatic

parameters of pruritis measured were panniculus response, arching of back and involuntary lifting of hind leg and attempting to scratch the hair. An empiric visual analogue scale (VAS) was employed with the dog's reactions graded from 0 to 3 depending on the severity of reaction; 0 equating to a negative response through to 3 indicating a high reactivity.

Immunological analysis

Flea antigen-specific IgE antibodies, as well as antibodies against numerous other antigens (see Table 1) were measured in serum using a commercial ELISA canine allergy test (Greer Laboratories, USA).

Semi-quantitative determination of IL-4, IL-5, IL-10 and IFN-γ mRNA gene expression in peripheral blood mononuclear cells was performed by RT-PCR, which is a well known and documented technique (Chamizo C et al. 2001; 83: 191-202). Histological assessment and cytokine analysis were determined on punch biopsies (2 mm deep skin sections) taken before and after treatment. Tissue sections were stained with hematoxylin and eosin (H&E) according to routine well know procedures, for the presence of inflammatory cells in the lesion. The levels of cytokine expression were determined by RT-PCR.

Figure 1 illustrates the individual clinical responses of the two dogs for each of the clinical symptoms of pruritis, across the 14 days of the study. As can be seen at the commencement of the study both animals exhibited overt signs of pruritis with both dogs exhibiting a VAS of 3 for all symptoms measured. Between days 4 and 8 each dog had started to show improvements in each of the clinical symptoms and by day 14 both dogs had ceased to exhibit clinical signs of the problem.

Allergen reactivity IgE test

Serum samples were tested against a panel of common allergens, including fleas, for IgE antibody by ELISA. As shown in Table 1 below, there was a significant drop in allergen reactivity for IgE across the board after treatment with *L. fermentum* compared to baseline levels in both dogs. In particular, following treatment there was a reduction in IgE antibody for flea antigens, which correlated with a reduction in clinical symptoms common to dogs infected with fleas. Without wishing to be bound by theory, this may

indicate a down-regulation of Th2 T-cell response associated with skin hypersensitivity.

Table 1: IgE antibody against common allergens

	BEAUJOLAIS			JAEGER		
ALLERGEN	%R Base	%R Test		%R Base	%R Test	
couch grass	77	63	-18%	110	100	-9%
johnson grass	80	66	-18%	104	90	-13%
blue grass	57	52	-9%	120	106	-12%
ryegrass	67	63	-6%	101	101	0%
cocksfoot	74	62	-16%	103	90	-13%
sweet vernel	70	59	-16%	105	90	-14%
yorkshire grass	66	49	-26%	109	90	-17%
canary grass	65	61	-6%	99	100	1%
paspalum species	68	63	-7%	101	100	-1%
prarie/broome grass	63	59	-6%	94	111	18%
oat grass	63	62	-2%	86	110	28%
english couch	70	62	-11%	106	110	4%
dock/sorrell	66	59	-11%	109	117	7%
pine	67	56	-16%	99	91	-8%
pigweed	56	52	-7%	124	114	-8%
chenopodium/fat hen	59	56	-5%	113	117	4%
english plantain	63	56	-11%	127	117	-8%
short ragweed	55	50	-9%	104	109	5%
western ragweed	50	44	-12%	121	119	-2%
dog fennel	66	56	-15%	119	108	-9%
housedust mite	22	21	-5%	52	62	19%
housedust	17	9	-47%	33	38	15%
fleas	48	36	-25%	119	100	-16%
wattle	69	60	-13%	114	113	-1%
casurina	75	56	-25%	107	117	9%
elm	58	44	-24%	119	119	0%
juniper	63	43	-32%	80	112	40%
birch	51	42	-18%	132	124	-6%
olive	62	49	-21%	116	108	-7%
oak	55	54	-2%	94	111	18%
melaleuca	64	62	-3%	134	134	0%
privet	71	52	-27%	113	130	15%
alternaria	48	46	-4%	86	82	-5%
aspegillus	101	114	13%	112	101	-10%
cladospoium	76	78	3%	83	79	-5%

From the results of this study it would appear that oral administration of *Lactobacillus fermentum* in the dogs feed was effective in the treatment of this form of dermatitis and in particular in resolving the clinical symptoms of pruritis.

Example 4: Case study 3 – treatment of acne.

Teenage (13 years old) identical male twins living in the same household, with developing acne were treated separately. Twin A was routinely administered with 2 capsules per day *L fermentum* VRI 002 in a capsule (10^{10} cfu per capsule) while twin B was not given any *L fermentum*. Both twins consumed the same diet and had similar routines. For the duration of the study (4 months), it was noted that Twin A had visibly less acne on the forehead and nose compared to twin B. The study was interrupted and twin B was given the *L fermentum* capsules as well because of the difference in the extent and severity of the acne.

Example 5: Treatment of eczema.

Case study 4:

Patient: 2 ½ yr old girl:

- Suffering from eczema for the past 6 months
- Elbow and knee joints inflamed, buttocks inflamed and weepy
- Has taken 4 courses of antibiotics over 2 years
- Does not have regular bowel movements (every 3 days)
- Diet: very high in wheat (pasta, bread), dairy (2 bottles a day of cow's milk), tomatoes

Started oral adminisration of *L. fermentum* VRI-002, at a dosage rate of ½ capsule morning and night. Mother noticed improvement in the first week of treatment

Follow up visit 2 weeks later:

- Eczema almost gone from knee and elbow joint
- No longer on buttocks
- Did appear for the first time on upper thoracic spine
- Treatment: will continue with *L. fermentum* for 3 months

Case study 5:

A 43 year old male patient presented with eczema in the form of an inflammed patch of skin on the palm of the left hand. Eczema was diagnosed

approximately 13 years earlier. Treatment over several years included corticosteroid creams and the like.

Treatment with *L fermentum* VRI 002 commenced with 2 capsules per day of (10^{10} cfu per capsule) and continued for 3 months. No other treatment was administered. Following 1 week of treatment with *L fermentum* the lesion resolved almost completely. Beneficial effects on nails and GI tract were also reported.

Case study 6:

Eighteen month old child (female) presented with eczema in the form of an inflammed area of skin of approximately 3 cm in diameter behind the right knee. The lesion has been in existence since shortly after birth and caused significant irritation and induced scratching. Treatment at presentation comprised application of a corticosteroid cream.

Treatment with the corticosteroid cream was suspended and treatment with *L fermentum* VRI 002 commenced with 1 capsule per day of (10^{10} cfu per capsule). No other treatment was administered. Following 1 week of treatment with *L fermentum* the lesion resolved completely. No side-effect of the *L fermentum* treatment were observed.

Case study 7:

Patient: Adult female who has suffered from eczema since the age of 9 or so. It slowly got worse over the years. The patient also suffered from suspected irritable bowel and Candida. A number of creams have been tried for her eczema. Initially a weak steroid cream was used, then progressed to Advantan ointment, a strong steroid cream. The patient was going through 3-5 small tubes per month. When the eczema was really bad, the patient took steroid tablets and also tried anti-bacterial creams which made it worse. UV light treatment was attempted by a dermatologist. There was some initial success but eczema never resolved and the treatment increased the itch. The patient anti-histamines sometimes (2-3 different types at a time). After a month or so, the anti-histamine needed to be rotated as one at a time, they became ineffective. At one point a dermatologist diagnosed infected eczema and recommended that the patient be hospitalised. Intended treatment was with immunosuppressants but the patient refused. No further assistance or treatment was offered

The patient was started on *L. fermentum* treatment, 6 capsules in the morning and 6 at night (2-10 billion cfu of *L. fermentum* per capsule).

. Following approximately one week of treatment there was a significant improvement in the severity of eczema. Although the treatment was not continued, there was a near total resolution of eczema in the first month following the treatment. Three months following the initial treatment the patient did not require further *L. fermentum* treatment.

Although the invention has been described with reference to specific examples, it will be appreciated by those skilled in the art that the invention may be embodied in many other forms.

REFERENCES

1. Dahl MV, Katz HI, Krueger GG, Millikan LE, Odom RB, Parker F, Wolf JE Jr, Aly R, Bayles C, Reusser B, Weidner M, Coleman E, Patrignelli R, Tuley MR, Baker MO, Herndon JH Jr, Czernielewski JM. Topical metronidazole maintains remissions of rosacea. Archives of Dermatology 1998. 134: 679 – 83.

2. Dahl MV, Jarratt M, Kaplan D, Tuley MR, Baker MD. Once-daily topical metronidazole cream formulations in the treatment of the papules and pustules of rosacea. Journal of the American Academy of Dermatology 2001. 45: 723 – 30.

3. Feldman SR, Hollar CB, Gupta AK, Fleischer AB Jr. Women commonly seek care for rosacea: dermatologists frequently provide the care. Cutis 2001. 68: 156 – 60.

4. Mahrle G, Bauermeister-Jasso K, Enderer K. Roaccutan in acne and rosacea. Z Hautkr 1985. 60: 120, 125 – 34.

5. Hoting E, Paul E, Plewig G. The treatment of rosacea with isotretinoin. International Journal of Dermatology 1986. 25: 660 – 3.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Method for prophylactic or therapeutic treatment of a skin disorder by administering to a subject requiring such treatment a therapeutically or prophylactically effective amount of a probiotic.

2. Method of treatment of one or more symptoms of a skin disorder by administering to a subject requiring such treatment an effective amount of a probiotic.

3. Method according to claim 1 or claim 2, wherein the skin disorder is dermatitis having associated therewith visible lesions.

4. Method according to claim 1 or claim 2, wherein the skin disorder is selected from the group consisting of contact dermatitis, actinic dermatitis, dermatitis caused by microbial infection, eczema and rosacea.

5. Method according to claim 1 or claim 2, wherein the subject to be treated is a household pet.

6. Method according to claim 5 wherein skin is flea-induced dermatitis.

7. Method according to any one of claims 2 to 6, wherein symptom to be treated is selected from pruritis, pain and erythema.

8. Method according to any one of claims 1 to 7, wherein the probiotic is a lactic acid bacterium.

9. Method according to claim 8, wherein the bacterium is *Lactobacillus fermentum*.

10. Method of lowering levels of one or more immune markers of allergy and/or inflammation in a subject with dermatitis having elevated levels of said markers, by administering to said subject an effective amount of a probiotic.

11. Method according to claim 10, wherein the immune marker is selected from immunoglobulins and/or cytokines characteristic of an allergic response or of Th1 and Th2 T cell response.

12. Method according to claim 11, wherein the marker is selected from IgE, IL-4, IL-10, IL-12, and interferon gamma.

13. Method according to any one of claims 1 to 12, wherein the probiotic is administered as a food or feed preparation or as a food or feed supplement.

14. Method according to any one of claims 1 to 12, wherein the probiotic is administered as a pharmaceutical composition.

15. Method according to any one of claims 1 to 14, wherein the probiotic is administered orally.

16. Method according to any one of claims 1 to 15, further comprising the administration of one or more pharmaceutically active agents used for treatment of skin disorders or dermatitis.

17. Method according to claim 16, wherein the probiotic, or a composition containing said probiotic, is administered simultaneously or sequentially with one or more pharmaceutically active agents.

18. Method according to any one of claims 8 to 17, wherein the amount of probiotic bacteria administered to a human subject is about 10^{10} bacteria.

19. Method according to any one of claims 8 to 17, wherein the amount of probiotic bacteria administered to a human subject is from about 10^{10} to about 10^{12} bacteria.

20. Method according to any one of claims 8 to 19, wherein the probiotic bacterium, or a composition containing said probiotic bacterium, is administered daily.

21. Dermatological composition comprising a therapeutically and/or prophylactically effective amount of a probiotic, optionally in conjunction with a pharmaceutically acceptable carrier, adjuvant, solvent or excipient.

22. Dermatological composition according to claim 21, wherein the probiotic is a probiotic bacterium *L. fermentum*.

23. Method for prophylactic or therapeutic treatment of a skin disorder by administering to a subject requiring such treatment a therapeutically or prophylactically effective amount of *Lactobacillus fermentum*.

24. Method of treatment of one or more symptoms of dermatitis by administering to a subject requiring such treatment an effective amount of *Lactobacillus fermentum*

25. Method according to claim 23 or claim 24, wherein the skin disorder is dermatitis having associated therewith visible lesions.

26. Method according to claim 23 or claim 24, wherein the skin disorder is selected from the group consisting of contact dermatitis, actinic dermatitis, dermatitis caused by microbial infection, eczema and rosacea.

27. Method according to claim 23 or claim 24, wherein the subject to be treated is a household pet.

28. Method according to claim 27 wherein skin is flea-induced dermatitis.

29. Method according to any one of claims 24 to 28, wherein symptom to be treated is selected from pruritis, pain and erythema.

30. Method of lowering levels of one or more immune markers of allergy and/or inflammation in a subject with dermatitis having elevated levels of said markers, by administering to said subject an effective amount of *Lactobacillus fermentum*

31. Method according to claim 30, wherein the immune marker is selected from immunoglobulins and/or cytokines characteristic of an allergic response or of Th1 and Th2 T cell response.

32. Method according to claim 30, wherein the marker is selected from IgE, IL-4, IL-10, IL-12, and interferon gamma.

33. Method according to any one of claims 23 to 32, wherein *Lactobacillus fermentum* is administered as a food preparation or supplement.

34. Method according to any one of claims 23 to 32, wherein *Lactobacillus fermentum* is administered as a pharmaceutical composition.

35. Method according to any one of claims 23 to 34, wherein *Lactobacillus fermentum* is administered orally.

36. Method according to any one of claims 23 to 35, further comprising the administration of one or more pharmaceutically active agents used for treatment of skin disorders or dermatitis.

37. Method according to claim 36, wherein *Lactobacillus fermentum*, or a composition containing *Lactobacillus fermentum*, is administered simultaneously or sequentially with one or more pharmaceutically active agents.

38. Method according to any one of claims 23 to 37, wherein the amount of *Lactobacillus fermentum* administered to a human subject is about 10^{10} bacteria.

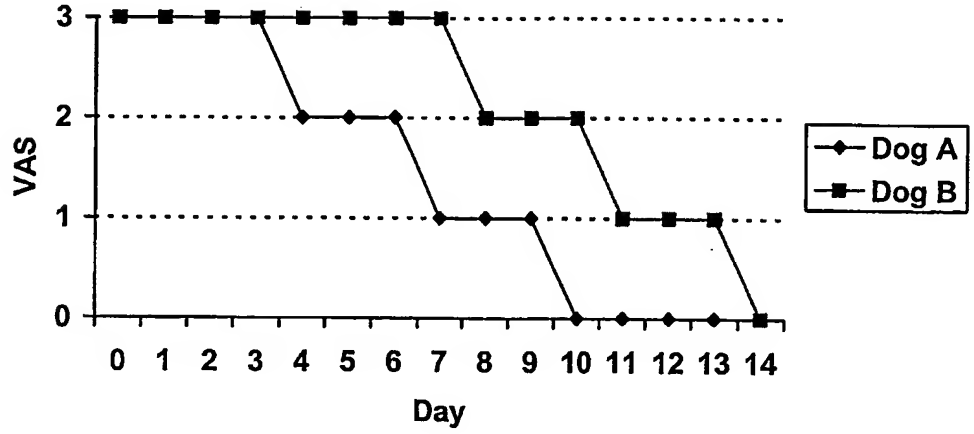
39. Method according to any one of claims 23 to 37, wherein the amount of *Lactobacillus fermentum* administered to a human subject is from about 10^{10} to about 10^{12} bacteria.

40. Method according to any one of claims 23 to 39, wherein *Lactobacillus fermentum*, or a composition containing *Lactobacillus fermentum*, is administered daily.

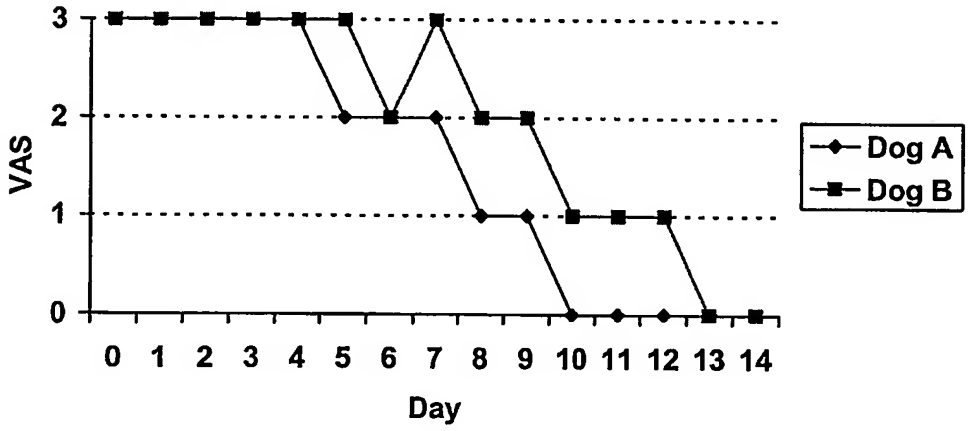
41. Dermatological composition comprising a therapeutically and/or prophylactically effective amount of *Lactobacillus fermentum*, optionally in conjunction with a pharmaceutically acceptable carrier, adjuvant, solvent or excipient.

Figure 1

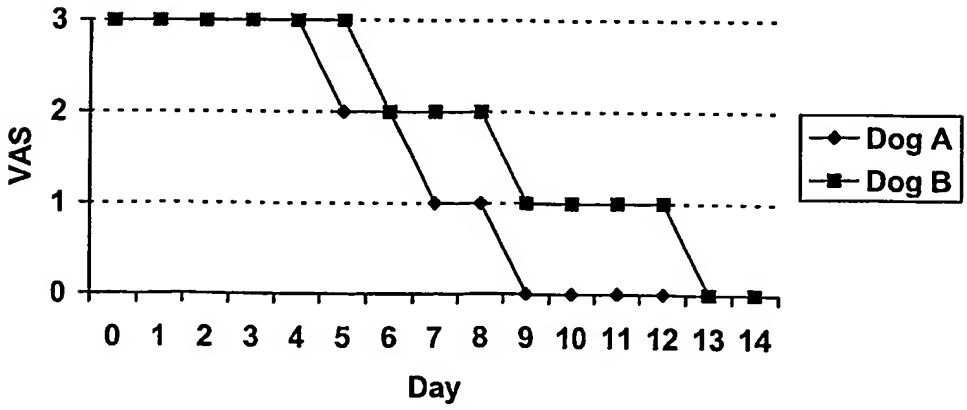
i) Panniculus



ii) Back Arching



iii) Involuntary Scratching



INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU03/00200

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: A61K 35/74, A61P 17/00, 17/04, 37/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC A61K

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT, MEDLINE: keywords; dermatitis, pruritis, skin, allergy, probiotic()bacteri+, rosacea, lactobacillus, fermentum, acidophilus.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN publication number 09-263539, (NICHINICHI SEIYAKU KK) 7 October 1997. See whole document.	1-8, 13-14, 18-21
X	PATENT ABSTRACTS OF JAPAN publication number 09-002959, (YAKULT HONSHA CO LTD) 7 January 1997. See whole document.	10-12, 30-32,41
X	WO 00/71139A (REID, G et al) 30 November 2000. See whole document.	1-3, 8,9, 14-17, 20-23, 41.

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 April 2003	24 APR 2003

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU03/00200

C (Continuation). **DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ISOLAURI, E et al, "Probiotics in the management of atopic eczema". Clinical and Experimental Allergy, 2000, Vol 30, pp 1604-1610. See whole document.	1-4, 7-8, 10, 21
X	MAJAMAA H et al, "Probiotics: A novel approach in the management of food allergy" The Journal of Allergy and Clinical Immunology Vol 99 (2), Feb 1997 pp179-85. See whole document.	1-4, 7-8, 10, 21
X	KALLIOMAKI, M et al, "Probiotics in primary prevention of atopic disease; a randomised placebo-controlled trial" The Lancet vol 357 April 7, 2001 pp 1076-1079. See whole document.	1-4, 7-8, 10, 21
X	MURCH, S.H, "Toll of allergy reduced by probiotics" The Lancet vol 357 April 7, 2001 pp1057-1059. See whole document.	1-4, 7-8, 10, 21
X	MOMBELLI, B et al, "The use of probiotics in medical practice" International Journal of Antimicrobial Agents Vol 16 (2000) pp531-536. See whole document.	10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU03/00200

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member	
WO	00/71139	AU	49054/00

END OF ANNEX